

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

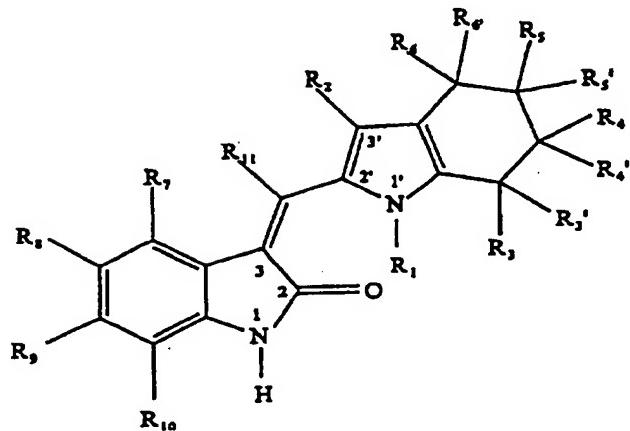
Listing of Claims:

1. – 6. (canceled)

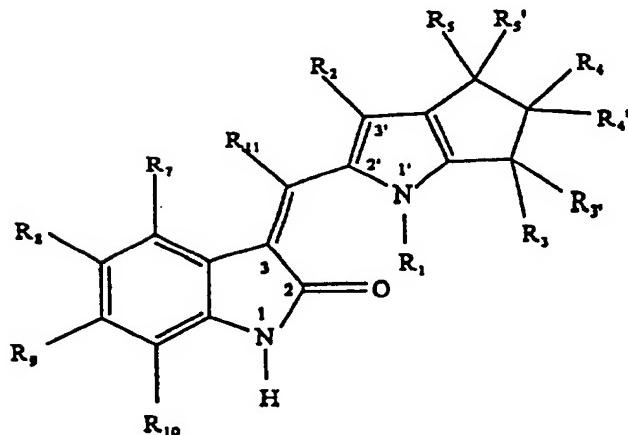
7. (original) An optionally substituted 3-[(tetrahydroindole-2-yl)methylene]-2-indolinone or 3-[(cyclopentano-*b*-pyrrol-2-yl)methylene]-2-indolinone compound.

8. (amended) The indolinone compound of claim 7 of formula XIX or XX,

XIX



XX



or a pharmaceutically acceptable salt, isomer, metabolite, ester, amide, or prodrug thereof
where (a) R₁ is selected from the group consisting of,

- (i) alkyl that is optionally substituted with a monocyclic or bicyclic five, six, eight, nine, or ten membered heterocyclic ring, where the ring is optionally substituted with one or more halogen, or trihalomethyl substituents;
 - (ii) five, six, eight, nine, or ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more halogen or trihalomethyl substituents;
 - (iii) ketone of formula -CO-R₁₂, where R₁₂ is selected from the group consisting of hydrogen, alkyl, or a five or six membered heterocyclic ring;
 - (iv) a carboxylic acid of formula -(R₁₃)_n-COOH or ester of formula -(R₁₄)_m-COO-R₁₅, where R₁₃, R₁₄, and R₁₅ are independently selected from the group consisting of alkyl or a five or six membered heterocyclic ring and n and m are independently 0 or 1;
 - (v) a sulfone of formula -(SO₂)-R₁₆, where R₁₆ is selected from the group consisting of alkyl or a five or six membered heterocyclic ring, where the ring is optionally substituted with an alkyl moiety;
 - (vi) -(R₁₇)_n-(indole-1-yl) or -(R₁₈)_m-CHOH-(R₁₉)_p-(indole-1-yl), where the indole moiety is optionally substituted with an aldehyde and R₁₇, R₁₈, and R₁₉ are alkyl and n, m, and p are independently 0 or 1;
 - (vii) taken together with a 2' substituent of the indole ring forms a tricyclic moiety, where each ring in the tricyclic moiety is a five or six membered heterocyclic ring;
- (b) R₂, R₃, R_{3'}, R₄, R_{4'}, R₅, R_{5'}, R₆ and R_{6'} are selected from the group consisting of,
- (i) hydrogen;
 - (ii) alkyl that is optionally substituted with a monocyclic or bicyclic five, six, eight, nine, or ten membered heterocyclic ring, where the ring is optionally substituted with one or more halogen, or trihalomethyl substituents;

- (iii) five, six, eight, nine, or ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more halogen or trihalomethyl substituents;
- (iv) ketone of formula -CO-R₂₀, where R₂₀ is selected from the group consisting of hydrogen, alkyl, or a five or six membered heterocyclic ring;
- (v) a carboxylic acid of formula -(R₂₁)_n-COOH or ester of formula -(R₂₂)_m-COO-R₂₃, where R₂₁, R₂₂, and R₂₃ are independently selected from the group consisting of alkyl or a five or six membered heterocyclic ring and m and n are independently 0 or 1;
- (vi) halogen;
- (vii) an alcohol of formula -(R₂₄)_m-OH or an ether of formula -(R₂₄)_n-O-R₂₅, where R₂₄ and R₂₅ are independently selected from the group consisting of alkyl and a five or six membered heterocyclic ring and m and n are independently 0 or 1;
- (viii) -NR₂₆R₂₇, where R₂₆ and R₂₇ are independently selected from the group consisting of hydrogen, oxygen, alkyl, and a five or six membered heterocyclic ring;
- (ix) -NHCOR₂₈, where R₂₈ is selected from the group consisting of hydroxyl, alkyl, and a five or six membered heterocyclic ring, where the ring is optionally substituted with alkyl, halogen, carboxylate, or ester;
- (x) -SO₂NR₂₉R₃₀, where R₂₉ and R₃₀ are selected from the group consisting of hydrogen, oxygen, alkyl, and a five or six membered heterocyclic ring;
- (xi) any two of R₃, R_{3'}, R₄, R_{4'}, R₅, R_{5'}, R₆, or R_{6'} taken together form a bicyclic or tricyclic heterocyclic moiety fused to the six membered ring of the indole, where each ring in the multicyclic moiety is a five or six membered heterocyclic ring;
- (c) R₇, R₈, R₉, and R₁₀ are independently selected from the group consisting of,
- (i) hydrogen;

- (ii) alkyl that is optionally substituted with a monocyclic or bicyclic five, six, eight, nine, or ten membered heterocyclic ring, where the ring is optionally substituted with one or more halogen, or trihalomethyl substituents;
- (iii) five, six, eight, nine, or ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more halogen or trihalomethyl substituents;
- (iv) ketone of formula -CO-R₃₁, where R₃₁ is selected from the group consisting of hydrogen, alkyl, or a five or six membered heterocyclic ring;
- (v) a carboxylic acid of formula -(R₃₂)_n-COOH or ester of formula -(R₃₃)_m-COO-R₃₄, where R₃₂, R₃₃, and R₃₄ are independently selected from the group consisting of alkyl or a five or six membered heterocyclic ring and n and m are independently 0 or 1;
- (vi) halogen;
- (vii) an alcohol of formula -(R₃₅)_m-OH or an ether of formula -(R₃₅)_n-O-R₃₆, where R₃₅ and R₃₆ are independently chosen from the group consisting of alkyl or a five or six membered heterocyclic ring and m and n are independently 0 or 1;
- (viii) -NR₃₇R₃₈, where R₃₇ and R₃₈ are independently selected from the group consisting of hydrogen, oxygen, alkyl, and a five or six membered heterocyclic ring;
- (ix) -NHCOR₃₉, where R₃₉ is selected from the group consisting of hydroxyl, alkyl, and a five or six membered heterocyclic ring, where the ring is optionally substituted with alkyl, halogen, carboxylate, or ester;
- (x) -SO₂NR₄₀R₄₁, where R₄₀ and R₄₁ are selected from the group consisting of hydrogen, oxygen, alkyl, and a five or six membered heterocyclic ring;

(xi) any two of R₇, R₈, R₉, or R₁₀ taken together form a bicyclic or tricyclic heterocyclic moiety fused to the six membered ring of the indole, where each ring in the multicyclic moiety is a five or six membered heterocyclic ring; and

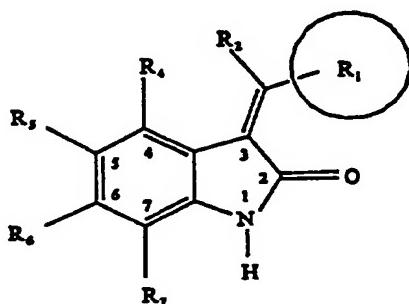
(d) R₁₁ is hydrogen or alkyl.

9. (amended) An indolinone compound having a substituent at the 5 position of the oxindole ring, where the substituent at the 5 position of the oxindole ring is selected from the group consisting of

- (a) alkyl that is optionally substituted with a monocyclic or bicyclic five, six, eight, nine, or ten membered heterocyclic ring, where the ring is optionally substituted with one or more halogen, or trihalomethyl substituents;
- (b) five, six, eight, nine, or ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more halogen or trihalomethyl substituents;
- (c) a ketone of formula -CO-R₁₀, where R₁₀ is selected from the group consisting of hydrogen, alkyl, or a five or six membered heterocyclic ring;
- (d) a carboxylic acid of formula -(R₁₁)_n-COOH or ester of formula -(R₁₂)_m-COO-R₁₃, where R₁₁, R₁₂, and R₁₃ are independently selected from the group consisting of alkyl or a five or six membered heterocyclic ring and m and n are independently 0 or 1;
- (e) halogen;
- (f) an alcohol of formula -(R₁₄)_m-OH or an ether of formula -(R₁₄)_n-O-R₁₅, where R₁₄ and R₁₅ are independently selected from the group consisting of alkyl and a five or six membered heterocyclic ring and m and n are independently 0 or 1;
- (g) -NR₁₆R₁₇, where R₁₆ and R₁₇ are independently selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring;

- (h) $-\text{NHCOR}_{18}$, where R_{18} is selected from the group consisting of alkyl, and a five or six membered heterocyclic ring, where the ring is optionally substituted with alkyl, halogen, carboxylate, or ester;
- (i) $-\text{SO}_2\text{NR}_{19}\text{R}_{20}$, where R_{19} and R_{20} are selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring;
- (j) any two of R_4 , R_5 , R_6 , or R_7 taken together form a bicyclic or tricyclic heterocyclic moiety fused to the six membered ring of the oxindole, where each ring in the multicyclic moiety is a five or six membered heterocyclic ring.

10. (amended) The compound of claim 9 of the following formula,



where (a) R_5 is selected from the group consisting of,

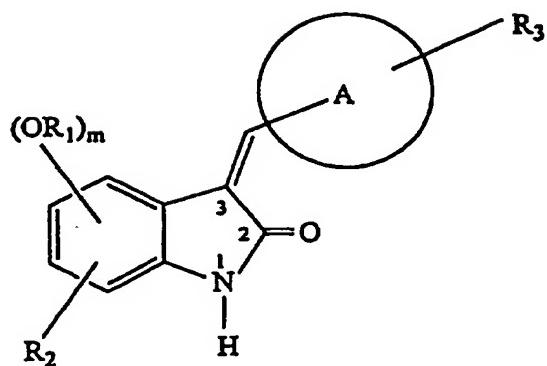
- (i) alkyl that is optionally substituted with a monocyclic or bicyclic five, six, eight, nine, or ten membered heterocyclic ring, where the ring is optionally substituted with one or more halogen, or trihalomethyl substituents;

- (ii) five, six, eight, nine, or ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more halogen or trihalomethyl substituents;
- (iii) a ketone of formula -CO-R₁₀, where R₁₀ is selected from the group consisting of hydrogen, alkyl, or a five or six membered heterocyclic ring;
- (iv) a carboxylic acid of formula -(R₁₁)_n-COOH or ester of formula -(R₁₂)_m-COO-R₁₃, where R₁₁, R₁₂, and R₁₃ are independently selected from the group consisting of alkyl or a five or six membered heterocyclic ring and m and n are independently 0 or 1;
- (v) halogen;
- (vi) an alcohol of formula -(R₁₄)_m-OH or an ether of formula -(R₁₄)_n-O-R₁₅, where R₁₄ and R₁₅ are independently selected from the group consisting of alkyl and a five or six membered heterocyclic ring and m and n are independently 0 or 1;
- (vii) -NR₁₆R₁₇, where R₁₆ and R₁₇ are independently selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring;
- (viii) -NHCOR₁₈, where R₁₈ is selected from the group consisting of alkyl, and a five or six membered heterocyclic ring, where the ring is optionally substituted with alkyl, halogen, carboxylate, or ester;
- (ix) -SO₂NR₁₉R₂₀, where R₁₉ and R₂₀ are selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring;
- (x) any two of R₄, R₅, R₆, or R₇ taken together form a bicyclic or tricyclic heterocyclic moiety fused to the six membered ring of the oxindole, where each ring in the multicyclic moiety is a five or six membered heterocyclic ring;
- (b) R₁ is selected from the group consisting of a five, six, eight, nine, and ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more substituents selected from the group consisting of

- (i) hydrogen and alkyl that is optionally substituted with a monocyclic or bicyclic five, six, eight, nine, or ten membered heterocyclic ring, where the ring is optionally substituted with one or more halogen, or trihalomethyl substituents;
 - (ii) five, six, eight, nine, or ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more halogen or trihalomethyl substituents;
 - (iii) a ketone of formula -CO-R₂₁, where R₂₁ is selected from the group consisting of hydrogen, alkyl, or a five or six membered heterocyclic ring;
 - (iv) a carboxylic acid of formula -(R₂₂)_n-COOH or ester of formula -(R₂₃)_m-COO-R₂₄, where R₂₂, R₂₃, and R₂₄ are independently selected from the group consisting of alkyl or a five or six membered heterocyclic ring and m and n are independently 0 or 1;
 - (v) halogen;
 - (vi) an alcohol of formula -(R₂₅)_m-OH or an ether of formula -(R₂₅)_n-O-R₂₆, where R₂₅ and R₂₆ are independently selected from the group consisting of alkyl and a five or six membered heterocyclic ring and m and n are independently 0 or 1;
 - (vii) -NR₂₇R₂₈, where R₂₇ and R₂₈ are independently selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring;
 - (viii) -NHCOR₂₉, where R₂₉ is selected from the group consisting of alkyl, and a five or six membered heterocyclic ring, where the ring is optionally substituted with alkyl, halogen, carboxylate, or ester;
 - (ix) -SO₂NR₃₀R₃₁, where R₃₀ and R₃₁ are selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring;
- (c) R₄, R₆, and R₇ are independently selected from the group consisting of,

- (i) hydrogen and alkyl that is optionally substituted with a monocyclic or bicyclic five, six, eight, nine, or ten membered heterocyclic ring, where the ring is optionally substituted with one or more halogen, or trihalomethyl substituents;
 - (ii) five, six, eight, nine, or ten membered monocyclic or bicyclic heterocyclic ring, where the ring is optionally substituted with one or more halogen or trihalomethyl substituents;
 - (iii) a ketone of formula -CO-R₃₂, where R₃₂ is selected from the group consisting of hydrogen, alkyl, or a five or six membered heterocyclic ring;
 - (iv) a carboxylic acid of formula -(R₃₃)_n-COOH or ester of formula -(R₃₄)_m-COO-R₃₅, where R₃₃ R₃₄ and R₃₅ are independently selected from the group consisting of alkyl or a five or six membered heterocyclic ring and m and n are independently 0 or 1;
 - (v) halogen;
 - (vi) an alcohol of formula -(R₃₆)_m-OH or an ether of formula -(R₃₆)_n-O-R₃₇, where R₃₆ and R₃₇ are independently selected from the group consisting of alkyl and a five or six membered heterocyclic ring and m and n are independently 0 or 1;
 - (vii) -NR₃₈R₃₉, where R₃₈ and R₃₉ are independently selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring;
 - (viii) -NHCOR₄₀, where R₄₀ is selected from the group consisting of alkyl, and a five or six membered heterocyclic ring, where the ring is optionally substituted with alkyl, halogen, carboxylate, or ester;
 - (ix) -SO₂NR₄₁R₄₂, where R₄₁ and R₄₂ are selected from the group consisting of hydrogen, alkyl, and a five or six membered heterocyclic ring; and
- (d) R₂ is hydrogen or alkyl.

11. (original) A compound having formula XXI, wherein:



XXI

- (a) A is a five or six membered ring comprised of atoms selected from the group consisting of oxygen, carbon, sulfur and nitrogen;
- (b) m is zero, 1, or 2;
- (c) R1 is hydrogen, C1-C6 alkyl or C2-C6 alkanoyl;
- (d) one of R2 and R3 independently is hydrogen and the other is a substituent selected from:
 - (1) a C1-C6 alkyl group substituted by 1, 2 or 3 hydroxy groups;
 - (2) SO3R4 in which R4 is hydrogen or C1-C6 alkyl unsubstituted or substituted by 1, 2 or 3 hydroxy groups;

- (3) SO_2NHR_5 in which R_5 is as R_4 defined above or a- $(\text{CH}_2)_n\text{-N}(\text{C}_1\text{-C}_6 \text{ alkyl})_2$ group in which n is 2 or 3;
- (4) COOR_6 in which R_6 is $\text{C}_1\text{-C}_6$ alkyl unsubstituted or substituted by phenyl or by 1, 2 or 3 hydroxy groups or phenyl;
- (5) CONHR_7 , in which R_7 is hydrogen, phenyl or $\text{C}_1\text{-C}_6$ alkyl substituted by 1, 2 or 3 hydroxy groups or by phenyl;
- (6) NHSO_2R_8 in which R_8 is $\text{C}_1\text{-C}_6$ alkyl or phenyl unsubstituted or substituted by halogen or by $\text{C}_1\text{-C}_4$ alkyl;
- (7) $\text{N}(\text{R}_9)_2$, NHR_9 or OR_9 wherein R_9 is $\text{C}_2\text{-C}_6$ alkyl substituted by 1, 2 or 3 hydroxy groups;
- (8) NHCOR_{10} , OOCR_{10} or $\text{CH}_2\text{OOCR}_{10}$ in which R_{10} is $\text{C}_1\text{-C}_6$ alkyl substituted by 1, 2 or 3 hydroxy groups;
- (9) NHCONH_2 ; $\text{NH-C}(\text{NH}_2)=\text{NH}$; $\text{C}(\text{NH}_2)=\text{NH}$; $\text{CH}_2\text{NHC}(\text{NH}_2)=\text{NH}$; CH_2NH_2 ; OPO(OH)_2 ; $\text{CH}_2\text{OPO(OH)}_2$; PO(OH)_2 ; or a



wherein X is selected from the group consisting of CH_2 , SO_2 , CO , or $\text{NHCO}(\text{CH}_2)_p$ in which p is 1, 2, or 3 and Z is CH_2 , O or $\text{N}-\text{R}_{11}$ in which R_{11} is hydrogen or is as R_9 defined above.

12. (original) A method of making an indolinone compound of any one of claims 5-11 comprising the steps of reaching an appropriate aldehyde and oxindole and separating the indolinone from the aldehyde and oxindole reactants.

13. (original) A pharmaceutical composition comprising (i) a pharmaceutically acceptable carrier or excipient and (ii) a compound according to any one of claims 5-11.

14. (original) A method for treating a disease related to unregulated tyrosine kinase signal transduction, the method comprising the step of administering to a subject in need thereof a therapeutically effective amount of a compound according to anyone of claims 5-11.

15. (original) A method for regulating tyrosine kinase signal transduction comprising administering to a subject a therapeutically effective amount of a compound according to any one of claims 5-11.

16. (original) A method of preventing or treating an abnormal condition in an organism, where the abnormal condition is associated with an aberration in a signal transduction pathway characterized by an interaction between a protein kinase and a natural binding partner, where the method comprises the following steps:

- (a) administering a compound of any one-of claims 5-11 to an organism; and
- (b) promoting or disrupting the abnormal interaction.

17. (original) A method of preventing or treating an abnormal condition in an organism, where the abnormal condition is associated with an aberration in a signal transduction pathway characterized by an interaction between a protein kinase and a natural binding partner, where the method comprises the following steps:

- (a) administering a compound of any one of claims 5-11 to an organism; and
- (b) promoting or disrupting the abnormal interaction.